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Summary

Many people feel that their morning coffee is necessary to get their day off to a good start. Caffeine is a well-accepted stimulant which generally increases alertness and improves performance but is not recommended as a pre-sleep drink. In contrast, the benzodiazepines are commonly used to induce sleep, but the next-day effect may be drowsiness and impaired performance, particularly at higher dose levels. The primary goals of this study were 1) to examine the effect of 250 mg caffeine (approximately two cups of coffee) on sleepiness, performance, and mood in a well-rested sample of good sleepers, and 2) to see if caffeine reduced the next-day hangover effects induced by a short half-life (triazolam (TRZ)) or a long half-life (flurazepam (FLZ)) benzodiazepine hypnotic. We also examined the relative impact of these two benzodiazepines at two dose levels, on subjective and objective measures of daytime sleepiness, on cognitive and psychomotor tasks, and on two measures of mood.

In a double-blind parallel group design, 80 young adult males were divided into eight treatment groups. Subjects received 15 or 30 mg of flurazepam, 0.25 or 0.50 mg of triazolam, or placebo at bedtime, and 250 mg of caffeine or placebo in the morning for two treatment days. Two objective (MSLT and lapses) and two subjective (Stanford Sleepiness Scale and Visual Analog) measures of sleepiness, five performance tests, and two mood measures (Profile of Mood Scale and Visual Analog Scale) were administered repeatedly on both days.

Significant treatment effects were found for sleepiness but not for performance or mood. Early morning caffeine significantly antagonized next day hypnotic induced drowsiness and enhanced alertness in the subjects who received bed time placebo. Flurazepam, 30 mg, subjects were more sleepy than all other groups, but the flurazepam, 15 mg, group did not differ significantly from those receiving triazolam.

Although not significantly different, the flurazepam, 30 mg, group had a poorer performance and more negative mood than the other groups. Performance in this group was most improved by caffeine. In all groups, sleepiness was greatest and performance and mood poorest in early morning trials, and caffeine was most effective at this time.



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Many people feel that their morning coffee is necessary to get their day off to a good start. Caffeine is a well-accepted stimulant which generally increases alertness and improves performance but is not recommended as a pre-sleep drink. In contrast, the benzodiazepines are commonly used to induce sleep, but the next-day effect may be drowsiness and impaired performance, particularly at higher dose levels. The primary goals of this study were 1) to examine the effect of 250 mg caffeine (approximately two cups of coffee) on sleepiness, performance, and mood in a well-rested sample of good sleepers, and 2) to see if caffeine reduced the next-day hangover effects induced by a short half-life (triazolam (TRZ)) or a long half-life (flurazepam (FLZ)) benzodiazepine hypnotic. We also examined the relative impact of these two benzodiazepines at two dose levels, on subjective and objective measures of daytime sleepiness, on cognitive and psychomotor tasks, and on two measures of mood.

Though daytime sleepiness is the most common complaint following nightly use of benzodiazepines, there have been relatively few objective studies and even fewer that have evaluated more than one dose level or more than one drug. The study by Ogura et al. (1980) is an exception. In a laboratory study, they compared next-day sleepiness from single doses of TRZ (0.25 mg and 0.50 mg) and FLZ (15 and 30 mg) in 16 healthy young adults. In a morning nap, sleep latency was significantly shorter and sleep time longer in the two groups that received FLZ when compared to placebo. This pattern was also seen in the afternoon and evening but differences were not significant. Although there was a trend for the TRZ group to also be more sleepy in the morning nap, they did not differ significantly from placebo. While Ss who received the high dose of FLZ were more sleepy than those receiving 15 mg, the subjects receiving 0.50 mg TRZ were more alert than those given 0.25 mg. The four groups did not differ on a subjective measure of sleepiness.

In a review of 45 studies, Greenblatt et al. (1984) found that complaints of central nervous system (CNS) depression, including drowsiness, occurred with increasing frequency with placebo, TRZ (0.25 mg), TRZ (0.50 mg), and FLZ (30 mg). In contrast, Gorenstein and Gentil (1983) using a subjective estimate of sleep, and Mitler et al. (1984) using the Multiple Sleep Latency Test (MSLT), found no significant between group differences in daytime sleepiness in groups receiving either a placebo, TRZ (0.50 mg) or FLZ (30 mg) the night before. Mitler et al. (1984), however, reported within group differences from

baseline for FLZ, but not for TRZ. Karacan et al. (1981) used the Stanford Sleepiness Scale (SSS) to examine three dose levels of FLZ (15, 26, and 45 mg) and reported a significant difference between the 15 and 45 mg doses.

The effects of benzodiazepines on next-day performance have been widely studied, and the review of 52 studies by Johnson and Chernik (1982) clearly indicated that, at some dose levels, all benzodiazepines given the night before impaired next-day performance. While the hypnotics with long half-life tended to produce more next-day impairment, they found that dose-level was the most important determinant. Tasks in which speed of performance was important were most likely to be impaired. Memory was also often impaired, especially with ingestion of a short half-life hypnotic. Since that review, no data have been published that contradict the general conclusions of Johnson and Chernik.

Investigators have reported both positive and negative next-day changes in mood following benzodiazepine hypnotic use. Studies that have reported significant next-day effects after nighttime ingestion of FLZ have found the subjects to be calmer (Bond and Lader 1973) and less unhappy (Karacan et al., 1981). Carskadon et al. (1982) found improvement in all scales of the Profile Of Moods Scale (POMS), except vigor, in the morning tests of elderly patients. Roth et al. (1977) and Church and Johnson (1979) reported no changes in mood following nighttime use of FLZ (30 mg) in normal young adults and Leibowitz and Sunchine (1978) found no next day changes in mood of insomniacs.

In contrast to the reports of a calming effect or no change with FLZ, studies of the effects of TRZ on next-day mood have reported feelings of anxiety and restlessness (Morgan and Oswald 1982; Kales et al., 1983). Borbely et al., (1983) however, found no such complaints after a single dose of 0.5 mg TRZ.

Caffeine's effects as a popular and proven stimulant have been reviewed by Dows (1982). When ingested near bedtime it has increased sleep latency [Goldstein et al., 1965; Brezinova, 1974; Karacan et al., 1976; Nicholson and Stone, 1981] and lowered arousal threshold during sleep (Bonnet et al., 1979).

Whether caffeine can be used to overcome the depressant effects of the benzodiazepines is unclear. Matilla et al. (1982) found that 250 and 500 mg of caffeine antagonized the effects of 10 mg of diazepam on the digit symbol substitution test (DSST), but performance was better with diazepam plus 250 mg of caffeine than diazepam plus caffeine, 500 mg. The lower dose of caffeine counteracted the effects of diazepam on the critical flicker fusion (CFF) test

30-minutes post ingestion but not after 90 minutes. The diazepam-induced calming effect was also counteracted by 500 mg of caffeine. Loke et al. (1985) found 3 and 6 mg/kg of caffeine reduced the deleterious effect of 0.15 and 0.30 mg/kg of diazepam on symbol cancellation but not on addition, card sorting, or immediate or delayed retention. In another study, 500 mg of caffeine counteracted the anxiolytic effects of 2.5 mg of lorazepam and 125-500 mg of caffeine reduced lorazepam-induced impairment in the symbol copying, but not the impairment in verbal learning (File et al. 1982). When Ghoneim et al. (1986) paired 6 mg/kg caffeine with .3 mg/kg diazepam, they found caffeine antagonized the diazepam effect on symbol cancellation and tended to reduce diazepam anxiolytic effects. Caffeine was less effective in antagonizing the diazepam induced impairment in addition and learning.

In the only laboratory study found that evaluated the ability of caffeine to counteract the sleep-inducing properties of a benzodiazepine, Roehrs et al. (1988) examined the effects of two dose levels of caffeine (4 mg/kg and 8 mg/kg) when paired with 0.50 mg TRZ in 12 healthy young adult males. The TRZ was administered at 0830 h and the caffeine at 1000 h and 1245 h. Neither dose of caffeine reversed TRZ's sleep-inducing effect nor did either dose reverse the immediate and delayed memory impairment produced by TRZ. However, caffeine (4 mg/kg) partially reversed the impairment on a performance battery administered at 1300 h and the 8 mg/kg dose completely reversed this impairment. We could find no study that evaluated the ability of caffeine to counteract daytime sleepiness and changes in performance and mood when the hypnotic was taken before bedtime and the caffeine was consumed early the next morning, the usual pattern in real life situations.

METHOD

Subjects:

Subjects (Ss) were 80 healthy young adult male volunteers, mean age 20.3 ± 2.74 , from the San Diego Naval School of Health Sciences. Ss were studied in pairs. Both Ss in a pair received the same treatment. Two pairs were replaced because of non-study related illness of one of the pair, and one pair was replaced because they were allowed to eat a much larger breakfast than called for in the protocol. Ss were nonsmokers and consumed no more than three cups of caffeinated beverage per day.

Subjects completed a health and sleep questionnaire, and only good sleepers were selected as the goal of this study was to evaluate next day behavior and not hypnotic efficacy. Interviews were conducted to ensure reliability of the questionnaire data and to explain the study. Urine and breathalyzer tests were done to ensure that Ss were drug-free. These tests were never positive.

Treatments:

The 80 subjects were randomly assigned in equal numbers to one of eight groups in a parallel-group, double-blind design. Each group received similar capsules at 2145 h and 0515 h on two nights. The evening and morning medications and dosages for the eight groups are listed in Table 1.

TABLE 1. Treatment groups

Group	Evening	Following Morning
PP	Placebo	Placebo
PC	Placebo	Caffeine
LTRZP	0.25 mg Triazolam	Placebo
HTRZP	0.5 mg Triazolam	Placebo
HTRZC	0.5 mg Triazolam	Caffeine
LFLZP	15 mg Flurazepam	Placebo
HFLZP	30 mg Flurazepam	Placebo
HFLZC	30 mg Flurazepam	Caffeine

Measures of Sleepiness:

Four measures of sleepiness were obtained during the day following each treatment night: two objective: Multiple Sleep Latency Test (MSLT) and lapses, and two subjective: Stanford Sleepiness Scale (SSS) and Visual Analog Scale (VAS).

MSLT:

Sleep latency was defined as the minutes from lights out to the appearance of the first sleep spindle, K complex or rapid eye movement (REM) sleep. Technicians were instructed to terminate the test one min after sleep occurred

and the test was ended after 20 min if sleep had not occurred. All MSLTs were scored blind by the first author. Because Richardson et al. (1978) and later Carskadon (1986) recommended that three consecutive, 30-s epochs of stage 1 be used as the indice of sleep latency, 13 MSLTs each for 20 Ss were scored using both stage 1 and stage 2 criteria. In this sample of good sleepers, the mean difference between the two measures was 1.3 ± 1.79 min. The three largest differences for the 260 tests were 14, 9, and 6 min. Most (145) differed less than one min, and in 83 instances, stage 1 sleep latency and stage 2 sleep criteria occurred on the same page. Occurrence of stage 2 or REM sleep was used for the analyses reported in the Results section.

Lapses:

This was a 10-min tapping task, five minutes with eyes closed, five minutes with eyes open. The S was instructed to relax but stay awake and to tap at a comfortable rate on a key beside his bed. The S was sitting up in bed. A lapse was scored when the time between taps was longer than three secs. Technicians were instructed to remind the S to keep tapping when a 5-10 s pause occurred. The number of lapses in the 10-min period was used as a measure of sleepiness. This task is a measure of the Ss' ability to remain awake and, in that respect, is similar to the Maintenance of Waking Test (MWT) of Mitler et al. (1982).

SSS-VAS:

The subjective estimates of sleepiness were obtained by use of the SSS (Hoddes et al. 1973) and by a 100 mm visual analogue scale (VAS). The sleep item was one of nine scales measuring various moods (Monk et al. 1985). On the VAS, the S was requested to draw a vertical line between very alert on the left end and very sleepy at the right end. The VAS score was measured in mm from 0 to 100. The SSS has seven steps ranging from (1) 'Alert, Wide Awake' to (7) 'Almost Asleep.' These measures were obtained before each MSLT.

Performance Tests:

The performance test battery included: 1) the Wilkinson 4-choice reaction time (CRT), 11 min, 2) digit symbol substitution test (DSST), 90 s, 3) card sorting by color, suit, and value, 4) short and long term memory and 5) a paired-associate learning task.

For the short-long term memory task, Ss heard a tape-recorded list of 15 words and wrote down each word. At the end of the 15-word presentation, the S had two minutes to write down as many words as he could recall. A new list was

given at each testing. Before the presentation of words for trial 4 at 1700 h, the S was first asked to recall the 45 words presented on the three previous trials and then to recognize the previously heard words from a list of 90 words. For the paired associate task the S learned 10 word-pairs from a tape-recorded list. The details of the lists and instructions were presented in Spinweber and Johnson (1982). Prior to learning a new pair of 10 words on trials 2, 3 and 4, the S was asked to recall the associates of the stem words given on the preceding trial. Two minutes were allowed for this recall. Prior to trial 4, the S was allowed two minutes to match the stem word from lists 1, 2, and 3 with their associates from a list of the previously presented associates.

Both computer and paper-pencil format were used. The CRT, short-term memory recall, and long-term memory recognition were presented by computer, the others by paper-pencil. The scores analyzed were mean RT for correct responses on CRT; total time in seconds required to complete the card sorting; the number correct on the DSST; the number correctly recalled and number recognized on short-term and long-term memory; and the number correctly recalled and recognized on paired associates.

Mood Measures:

Mood was evaluated by the POMS and the 9-item Visual Analog Mood Scale (Monk et al. 1985). The item "how sleepy do you feel" was omitted in computing the total VAS mood score. The score for each item was the distance in millimeters (mm) marked from the left end of a 100 mm line. Both the VAS mood items and the POMS scales were scored so that a high score reflected a more negative mood. Separate scale scores and total mood disturbance score were analyzed for the POMS and for VAS mood.

Procedure:

Pairs of Ss spent two-and-one-half days and two nights in the laboratory. All meals were provided and no caffeinated beverages were allowed. Breakfast consisted of orange juice, milk, and two pieces of buttered toast. Breakfast was at 0930 h, lunch at 1330 h, and the evening meal was at 1730 h. The late breakfast was to minimize the possible effect of food on caffeine in the early morning tests. In most instances, Ss reported to the laboratory around 1300 h on Monday. At that time, they received detailed information as to the nature of the study, study procedures and signed an informed consent statement. A

pretreatment training session was then conducted. Ss performed all the cognitive and psychomotor tests, and were given an MSLT usually between 1530-1630 h. Bedtime on each evening was 2150 h (lights out at 2200 h) and morning awakening was at 0500 h both days. The nighttime capsule was given at 2145 h and the morning capsule was administered at 0515 h. Testing times for the sleep performance and mood variables are listed in Table 2.

TABLE 2. Testing schedule: Day 1 - Day 2

MSLT VAS-SSS	LAPSES (TAPPING TASK)	PERFORMANCE-MOOD
0700	0600	0730
0900	1000	1130
1100	1400	1530
1300		1930
1500		
1700		

STATISTICAL ANALYSIS

Multivariate Analysis:

In this study, four sleep measures, five performance measures and two measures of mood, each with subscales, were collected three to six times a day over two days. To capitalize on the correlation among measures and to obtain an overall measure of significance, the initial analysis was a multivariate analysis of variance (MANOVA) for repeated measures computed for the sleepiness, the performance and the mood measures. Factors were treatment (groups), time (trials), and day. As time of day was of particular interest, a MANOVA was also computed for each trial with treatment F values being of primary interest.

The tapping task was not administered in the late afternoon, and thus lapses were not available for trial 4 in the composite sleepiness score for that trial. Also, the tapping task was administered at different times than other sleep measures (see Table 2). For statistical analysis, the 0700 h data for MSLT, VAS, and SSS were paired with 0600 h lapses (Trial 1), the averages of the 0900 h and 1100 h scores for MSLT, VAS, SSS were compared with the 1000 h lapse score (Trial 2), and the average of MSLT, VAS, SSS at 1300 h and 1500 h trials

were paired with 1400 h lapses (Trial 3). The MSLT, VAS, and SSS scores at 1500 h were used in Trial 4.

Univariate Analysis:

To examine the treatment sensitivity of each of the sleep measures, the performance measures and the mood measures, an analysis of variance (ANOVA) for repeated measures was computed for the separate sleep and performance measures and for the subscales of the POMS and individual items on the visual analog mood scale. The factors were group, trials, and day.

Pairwise Comparisons:

To reduce the likelihood of committing a type I error, the post-hoc pairwise analysis was preplanned. Pairwise comparisons focused on the goals of examining drug, dose-level effects, and the effects of caffeine. For the drug and dose-level questions, we compared the four drug groups without caffeine to placebo, the drug groups with each other, and the two dose-level groups for each drug. The effects of caffeine were examined by comparing the three caffeine groups with their respective control groups, e.g., HTRZC vs HTRZP, HFLZC vs HFLZP, PC vs PC, and all groups who received caffeine were compared with the PP group.

Hotelling T^2 was used to examine pairwise comparisons between groups and between trials. The .05 level was used for significance. Two-tailed tests were used except for preplanned pairwise comparison which were one-tailed. On the MANOVA and ANOVAs for repeated measure, the Geisser-Greenhouse conservative probability values were used.

Examination of the treatment scores for each group was made for statistical outliers. An outlier was defined as a score more than two standard deviations from the mean and the next lesser score was at least one standard deviation closer to the mean. One S in the HTRZP group met the criteria for his composite sleepiness score and VAS sleepiness score. This S was omitted from the analysis of sleep data, but was included in all other analyses. Omission of this S did not change any of the results from the MANOVA or ANOVA analyses. The only effect was in some of the pairwise comparisons of the HTRZP group with other groups. Omission of this S produced results more consistent with previous findings.

RESULTS

SLEEPINESS

Pretreatment:

To determine the pretreatment alertness of our sample, we calculated the pretreatment mean values for each sleep variable. These values were: MSLT 10.7 ± 5.7 (min); lapses 5.6 ± 5.9 , (number); VAS: 55.5 ± 22 (mm); and SSS 3.0 ± 1.2 .

We also examined whether pretreatment sleep scores were predictors of sleepiness during treatment irrespective of the type of treatment received. Correlation coefficients were calculated between the base line measurements for each variable and the mean of all the treatment measurements of that variable. Our results indicated a positive relationship for all variables. The correlation coefficients were for MSLT, $r = .49$, lapses, $r = .43$, VAS, $r = .29$ and SSS, $r = .33$. All p values were $<.01$. Because of the possible influence of pretreatment values on treatment response and since there were significant pretreatment group deficiencies for the MSLT, we computed our results using both difference scores (pretreatment minus treatment) and raw scores. As both analyses gave similar results, and as our groups were randomly assigned, only the raw score analysis is presented.

Treatment:

Repeated Measures MANOVA:

The means and standard deviations (SD) for the composite sleepiness score for each group are presented in Table 3. Each Ss composite sleep score was the mean of the four sleep measure values. For the MSLT, the score used was 20 minus sleep latency so that for all the measures a high score indicated greater sleepiness. The group means were based upon all the scores over all trials both days; the day scores were summed over trials, and the trial scores were for Days 1 and 2 combined. For day and trials, scores were summed over groups.

The PC group was the most alert and the HFLZP the most sleepy. The mean values for Days 1 and 2 were similar. Ss were clearly more sleepy on the early morning trial.

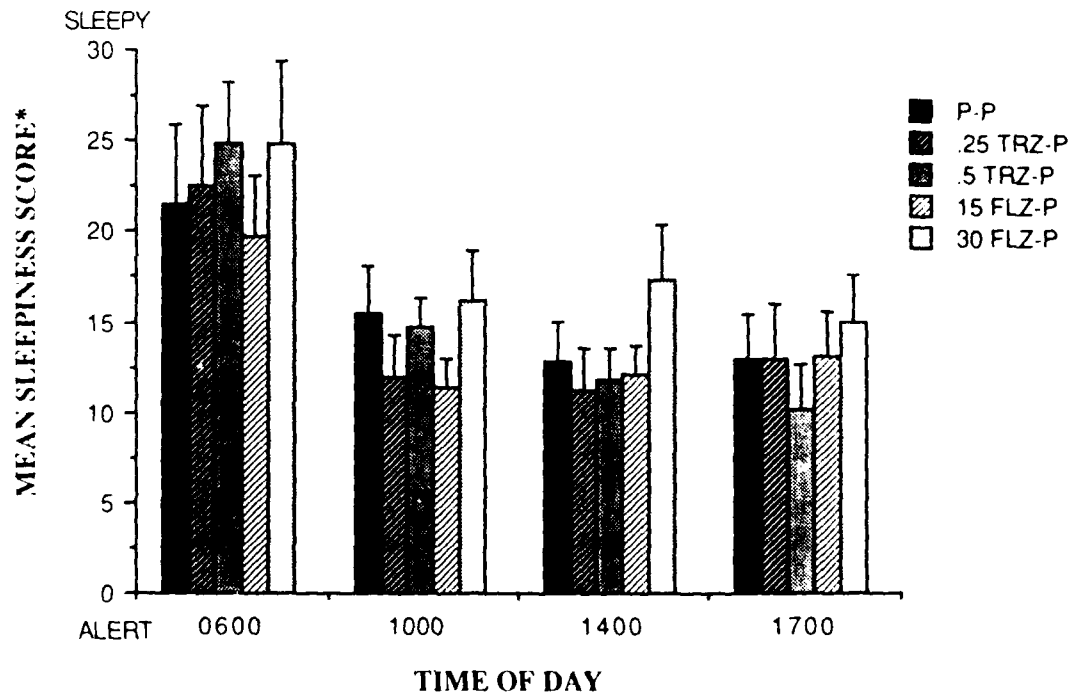
The F value for groups (treatments) was significant [$F(7,66) = 4.25$; $p < .001$]. The F value for trials (time of day) was also significant ($F(2,66) = 85.62$, $p < .001$). The MANOVA program requires complete

data in each cell. Due to technical problems, six Ss had missing lapses data, two in PP, one in LTRZP, two in HTRZC, one in HFLZP on one or more trials, and no lapse data were available for trial 4. Thus, the df was reduced to 66 and trial 4 was not included. Trial 4 was analyzed in the MANOVA for individual trials. The F value for day was not significant

TABLE 3. Means and Standard Deviations for composite sleepiness scores derived from 4 sleep measures. For groups the composite scores were summed over all trials both days; for days combined group scores were summed over trial for each day; for trials combined group scores were summed over days for each trial. A high score indicates greater sleepiness.

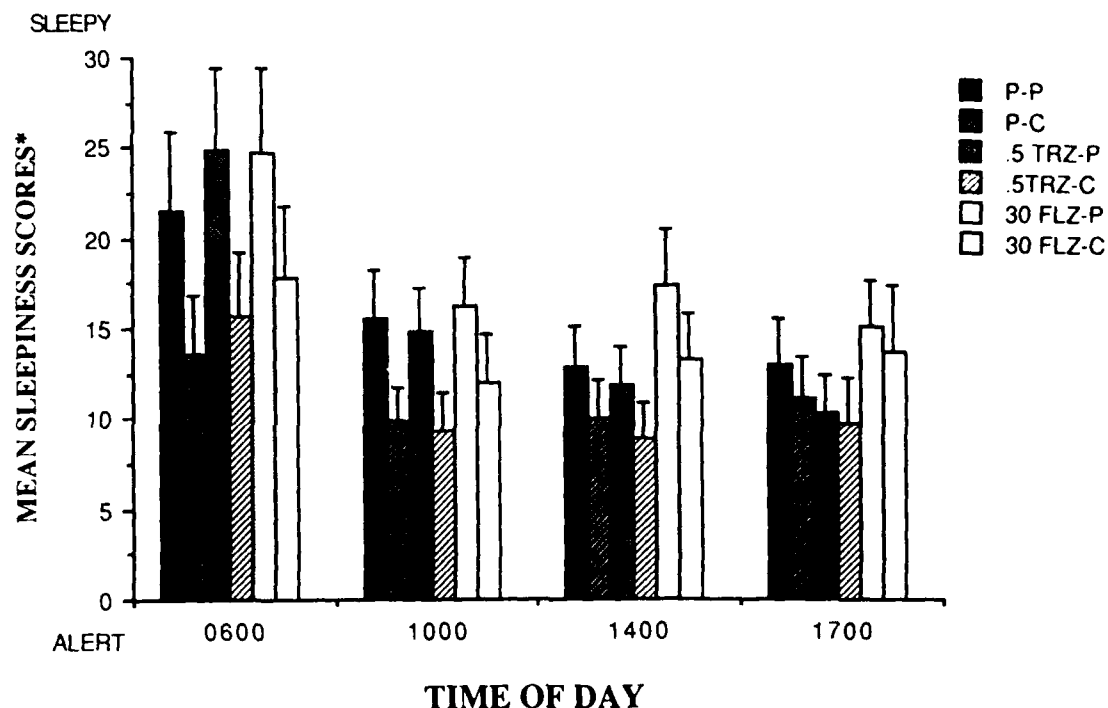
GROUP	MEAN	STD DEV
PP	16.5	21.85
PC	11.1	16.29
LWTRIAZP	15.0	20.16
HITRIAZP	17.2	20.22
HITRIAZC	11.8	17.33
LFLURAZP	14.4	15.71
HFLURAZP	19.5	23.40
HFLURAZC	15.2	22.03
<u>DAY</u>		
1	14.8	19.51
2	15.4	20.28
<u>TRIAL</u>		
T1	20.4	25.94
T2	12.7	15.56
T3	12.2	15.22
T4	12.2	14.65

nor were the day x group or day x trial x group interactions. The Trial x Group interaction, however, was significant, $F(14,128) = 2.33$, $p < .01$. This interaction reflected the differing patterns of alertness in the drug groups over the day. As the day progressed, sleepiness in the TRZ Ss decreased more rapidly than did sleepiness of Ss receiving FLZ, especially those receiving FLZ (30 mg). The HTRZP were more sleepy than LTRZP in the morning but were less sleepy than LTRZP later in the afternoon trials (see Figures 1 and 2).



*MSLT, LAPSES, VAS, SSS

Figure 1 Daytime sleepiness: Drugs and dose level effects. Means and SEMs for composite sleepiness values for groups who received a hypnotic at bedtime and a placebo in the morning.



*MSLT, LAPSES, VAS, SSS

Figure 2 Daytime sleepiness: Effects of caffeine. Means and SEMs for composite sleepiness values for groups who received a hypnotic at bedtime and caffeine in the morning.

Pairwise Comparisons:

The significant preplanned pairwise comparisons are listed in Table 4.

Caffeine produced the most consistent effect. All of the groups who received caffeine in the morning were significantly more alert than their comparison group. The HTRZC, but not the HFLZC group, were significantly more alert than the PP group. Both the LTRZP and HTRZP group were significantly less sleepy than the HFLZP but not the LFLZP Ss. The only significant dose level effect was between HFLZP and LFLZP.

TABLE 4. Significant Hotelling T^2 preplanned pairwise comparisons of the mean composite sleepiness scores. The most alert group is listed first in each pair.

GROUPS	P VALUE*
PC vs PP	.012
HTRZC vs PP	.025
HTRZC vs HTRZP	.027
HFLZC vs HFLZP	.011
LTRZP vs HFLZP	.028
HTRZP vs HFLZP	.049
LFLZP vs HFLZP	.011

*One tailed

MANOVA For Trials:

As there were no significant day effects or day x group interactions, for this analysis Day 1 and Day 2 scores were averaged. As noted earlier, for trials 1, 2, and 3, data from all four sleep variables were used. On trial 4, only MSLT, VAS and SSS data were available. The mean and SEM composite values for drug and dose level effects are presented in Fig. 1 and those for caffeine effects in Fig. 2. There were significant group differences for the first three trials: the respective F values were 4.43, $p < .001$; 3.19, $p < .006$; 3.55, $p < .003$. The df for all trials were 7.71. The percent reduction of sleepiness by caffeine for each trial is presented in Table 5. Caffeine effect was apparent through 1400 h, especially for the HFLZC group.

Pairwise Comparisons by Trials:

The significant Hotelling T^2 comparisons for trials 1, 2, and 3 are listed in Table 6. There were no significant group differences in trial 4 (1700h). On trials 1 and 2, the three caffeine groups were significantly more alert than their comparison group. On trial 3, PC was still

significantly more alert than the PP group, but when the HTRZC and HFLZC groups were compared with HTRZP and HFLZP, the p levels were .064 and .063 respectively. There was also a significant difference between LFLZP and HFLZP on all three trials. The groups receiving TRZ were less sleepy than those receiving FLZ. On trial 2, the LTRZP Ss were significantly more alert than HFLZP, and on trial 3, LTRZP was significantly less sleepy than both FLZ groups.

TABLE 5. Percent reduction of sleepiness by caffeine by time of day

GROUP	TRIALS			
	1	2	3	4
PLACEBO	38	36	17	14
TRZ .5 mg	31	31	20	0
FLZ 30 mg	29	25	26	9

Univariate Analysis:

To examine the relative contribution of each of the four sleep variables to the MANOVA results, a univariate ANOVA for repeated measures was computed for each variable with group, day, and time as factors. There were significant group effects for MSLT ($F = 4.65$, $p < .001$) and lapses ($F = 3.2$, $p < .005$), but not for the two subjective measures although, the VAS approached significance, ($F = 1.91$, $p < .080$). The dfs for all values were 7,71. There was a significant day effect only for number of lapses, but the day x group interaction was not significant. There was a significant time of day (trial) effect for all variables, but the trial x group interaction was not significant. All Ss were more sleepy on trial 1.

Summary: There was a significant treatment effect for daytime sleepiness primarily due to the caffeine vs comparison group differences. The treatment effect varied with time of day but not between days. All Ss were most sleepy in the early morning, and it was at this time that caffeine had its greatest effect. Ss who received a placebo at bedtime and caffeine in

Table 6. Hotelling T^2 pairwise comparisons by trial. Group listed first was most alert.

GROUP	P VALUE*
<u>TRIAL 1</u>	
PC vs PP	.012
HTRZC vs HTRZP	.024
HFLZC vs HFLZP	.005
LFLZP vs HFLZP	.022
<u>TRIAL 2</u>	
PC vs PP	.004
HTRZC vs PP	.015
HTRZC vs HTRZP	.031
HFLZC vs HFLZP	.038
LTRZP vs HFLZP	.007
LFLZP vs HFLZP	.000
<u>Trial 3</u>	
PC vs PP	.020
HTRZC vs PP	.005
LTRZP vs PP	.016
LTRZP vs LFLZP	.013
LTRZP vs HFLZP	.008
LFLZP vs HFLZP	.017

*One tailed

the AM were more alert than all other groups. There were no significant differences between drugs during the early morning trial, but as the day progressed, drug group differences began to appear because the TRZ Ss level of alertness increased more rapidly than did that for FLZ Ss. Significant dose-level effects were found only for FLZ. The MSLT and lapses were most sensitive to treatment effects. The SSS was least sensitive.

PERFORMANCE

Multivariate Analysis for Repeated Measures:

In contrast to the significant treatment effects for daytime sleepiness, there were no significant effects of either drug, at any dose level, or of caffeine on the composite performance score. The composite score was the mean of scores on all performance tasks. The MANOVA for repeated measures

that included all eight groups and the composite performance measure with treatment, day, and trial as factors, yielded only a trend toward a significant treatment effect, $p < .07$). Practice effects resulted in both a significant trial effect, $p < .001$, and a significant day effect, $p < .001$. The p values for the trial \times group and day \times group interactions were $< .10$ and $< .065$ respectively. The day \times trial \times group interaction did not approach significance.

When the MANOVA was done for each trial on both days, with groups as the primary factor, only the F value for trial 1, Day 2 approached significance ($F(7,72) = 2.09$, $p < .059$). There was a significant performance effect (task differences) for each trial, but none of the task \times group interactions were significant.

Pairwise Comparisons:

Even though these comparisons were preplanned and the results appear reasonable, the lack of significant MANOVA F values suggest that the results should be interpreted cautiously.

Drug Dose Level Effects: On Day 1, trial 1, the PP group performed significantly better than both HTRZP ($p < .023$, and HFLZP, $p < .011$). On both days, the poorest performers, compared to all groups, were the HFLZP subjects.

Caffeine Effects: Caffeine significantly antagonized the effects of HFLZP on trial 1, Day 1, $p < .002$. On Day 2, trial 1, the HFLZC vs HFLZP difference approached significance, $p < .0575$. The percent increase in performance by caffeine by time of day summed over Day 1 and Day 2 is presented in Table 7.

TABLE 7. Percent increase in performance by caffeine by time of day

GROUP	TRIALS			
	1	2	3	4
Placebo	1.5	4.5	6.5	0.5
TRZ .5 mg	10.0	7.0	5.5	6.0
FLZ 30 mg	22.0	14.0	12.0	10.5

Multivariate Analysis of Individual Performance Tests:

The results were similar to those of the composite score MANOVA. There were no significant group F values. A significant day and trial effect was found for card-sorting, CRT, and DSST reflecting the expected practice effects. The day x group interactions were not significant, but trial x group F-values were significant for DSST, $p < .01$ and CRT, $p < .05$. As with the sleepiness data, the interaction reflected the variability in performance from trial to trial in the hypnotic groups. As the day progressed, the groups that received TRZ improved their performance more rapidly than did the groups that received FLZ, especially HFLZP. Also, the HTRZP groups performance passed that of the LTRZP.

Summary: HFLZP subjects generally performed worse than all groups, but none of the hypnotic drugs nor caffeine had a significant effect on overall performance and there were no significant dose level effects. Caffeine was most helpful to Ss who received FLZ. Analysis of individual performance tasks also demonstrated no significant group differences. There was a practice effect for most tasks, and a significant trial X group interaction was found for DSST and CRT. HTRZP and HFLZP performed significantly worse than PP on the composite performance measures on Day 1, trial 1.

MOOD

The POMS and VAS (mood) scales were analyzed separately. MANOVA for repeated measures for POMS and for VAS (mood) yielded only one significant F value ($p < .001$, both scales) for trials. Mood became less negative during the day on both POMS and VAS mood. There were no significant day x group or trial x group interactions. Univariate analysis of the individual items in the VAS mood yielded results similar to the MANOVA. Only trial was significant; P value for trial was $< .001$. Univariate ANOVA of individual POMS scales also indicated no significant group effect. There were significant day effects for fatigue and vigor and trial effects for confusion and vigor. All p values were $< .01$. Mood was poorest in the morning. There were no significant interaction terms.

Pairwise Comparisons:

Hotelling's T^2 , based upon MANOVA data, yielded a significant difference between LFLZP and HFLZP on the composite VAS mood scale score. The HFLZP subjects had more negative mood. Again, these comparisons should be viewed with caution as there was not a significant group effect on the MANOVA.

Summary: Mood was generally unaffected by the treatments. None of the MANOVA analyses yielded significant treatment or interaction values, though a time effect was seen. A more negative mood was seen in the early morning trial. Generally the HFLZP subjects rated their mood as more negative and a FLZ dose level effect was seen. The moods of TRZ and especially the HTRZP subjects did not differ from the other subjects.

DISCUSSION

Caffeine (250 mg) was effective in reducing next-day sleepiness in Ss who had received FLZ (30 mg) or TRZ (0.5 mg) the night before. Caffeine also increased daytime alertness in a group who had received a placebo the previous night. Caffeine reduced the performance impairment in the two drug groups, especially in the group that received 30 mg FLZ, but the improvement in performance was not statistically significant. Neither the hypnotics or caffeine had a significant effect on mood.

Ss receiving FLZ were more sleepy than those receiving TRZ and the placebo group. But the differences were significant only when comparisons were made with the HFLZP group. The high dose of FLZ caused significantly more next day sleepiness than did the low dose. The two TRZ groups did not differ in sleepiness over the next day. In the early morning, the HTRZP group were more sleepy than LTRZP Ss, but as the day progressed this relationship was reversed.

As noted earlier, caffeine has generally been found to increase sleep latency and reduce total sleep time (TST) when administered prior to bedtime (Goldstein et al. (1965), Brezinova (1974), Karacan et al. (1976) and Nicholson and Stone (1981). Lipschutz et al. (1988) reported that caffeine, 250 mg, administered to sleepy subjects, MSLT <10 min, at 0900 and 1300 h significantly increased MSLT sleep latency when compared to placebo and this increased alertness was present 2.75 hours after caffeine ingestion. Roehrs et al. (1988) reported that caffeine (4 mg/kg and 9 mg/kg) did not reduce MSLT sleep latency in Ss who had received TRZ (0.5 mg), one and one-half hours before caffeine was given.

To our knowledge, ours is the only study that looked at the effect of morning caffeine on daytime alertness following nighttime hypnotic use. We can, however, compare the results of our PC group with those of Lumley et al. (1987). Daytime sleepiness/alertness was examined after 4.0 mg/kg of caffeine was administered to 18 normal young adult Ss between 0920-0950 h and

MSLTs were recorded at 1000, 1200, 1400 and 1600 h. Their Ss had spent either, 5, 8, or 11 hours in bed the previous night. Caffeine significantly increased sleep latency when compared to ethanol. In contrast to ethanol, where time in bed was a factor in next day sleep latency, sleep latency was similar for all three bedtimes in the caffeine Ss. They, like we, found that the effects of caffeine diminished over the day, reflecting its 3-7 hour half-life (Goodman et al. 1985).

Though caffeine was effective in antagonizing hypnotic-induced daytime sleepiness and increased alertness in the placebo group, this increased alertness was not reflected in significantly better performance or mood. Even so, a 22% increase in performance was seen in the HFLZC group at 0730 h. This 22% increase was twice that seen in the HTRZC group, and 15 times larger than that in our PC group. Caffeine, thus, was most effective in the most impaired. As with sleepiness, the caffeine was most effective in the early morning.

The direction of our drug and dose level effects on performance were consistent with most previous findings. FLZ (30 mg) produced most impairment and the decrement was consistently larger than that for FLZ (15 mg), and the two TRZ dose levels. HTRZP showed a larger decrement than PP and LTRZP in the morning, but the relative difference changed over the day. In contrast to the reports of Morgan and Oswald (1982) and Kales et al. (1983), our TRZ Ss, at both doses, reported no more negative feelings than other Ss. In this study, it was the HFZP Ss who reported the most negative feelings.

The lack of any significant caffeine effect on performance and mood was probably not due to the caffeine dose level. Dose levels lower than ours, even as low as 64 mg, have been found to significantly enhance performance and daytime alertness (Lieberman et al. (1987). Matilla et al. (1982) found a 250 mg dose more effective than a 500 mg dose in antagonizing the diazepam-induced performance decrement. Matilla et al. (1982) and File et al. (1982), however, found that a 500 mg dose of caffeine significantly antagonized the subjective calming effect of diazepam. Loke et al. (1985) reported that higher doses of caffeine increased hand tremor, especially on difficult tasks. Thus, doses higher than 250 mg appear contraindicated if the next day tranquilizing effect of the hypnotics is desired. Tremor at the higher dose may be a factor in the subjective reports of caffeine jitters.

Our failure to find improved performance after caffeine ingestion joins the growing list of inconsistent results. Of all the possible reasons for differing results (tasks, dose level, subjects, motivation, state), motivation and state were probably most important in our study. Our Ss were well-rested, good sleepers. Our pretreatment MSLT mean latency of 10.7 min is similar to those of Levine et al. (1988) who reported a mean sleep latency of 11.1 min for 129 young adults and 9.9 min for 76 college students. Our subjects were motivated to do well, as participating in our study was viewed as "good duty." The increase in performance seen in the HFLZC Ss suggests, however, that if a condition had existed that would have produced greater impairment, e.g., sleep loss or a stronger hypnotic effect, caffeine might have improved performance more.

The sensitivity of the MSLT to our treatments further indicates the usefulness of this measure of physiological sleep tendency. In contrast, the lack of sensitivity of the SSS raises further questions as to its interpretation as a measure of sleepiness, its relationship to MSLT and in a broader context, the relationship between objective and subjective sleep measures. Dement et al. (1978), Seidel et al. (1984), and Chordore et al. (1986) have found no significant relationship between subjective measures, mostly SSS, and the MSLT. We also found no significant relationship between the subjective and objective sleep measures used in this study (Johnson, et al. 1988). The MSLT is viewed as a measure of physiological sleep tendency (Carskadon & Dement 1982) and less subject to the influence of motivation and need to deny sleepiness than are the subjective measures, such as the SSS. For those who need a more easily obtained objective measure of sleepiness, the lapse test may be an alternative to the MSLT.

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<p>In a double-blind parallel group design, 80 young adult males were divided into eight treatment groups. Subjects received 15 or 30 mg of flurazepam, 0.25 or 0.50 mg of triazolam, or placebo at bedtime, and 250 mg of caffeine or placebo in the morning for two treatment days. Two objective (MSLT and lapses) and two subjective (Stanford Sleepiness Scale and Visual Analog) measures of sleepiness, five performance tests, and two mood measures (Profile of Mood Scale and Visual Analog Scale) were administered repeatedly on both days.</p> <p>Significant treatment effects were found for sleepiness but not for performance or mood. Early morning caffeine significantly antagonized next day hypnotic induced drowsiness and enhanced alertness in the subjects who received bed time placebo. Flurazepam, 30 mg, subjects were more sleepy than all other groups, but the flurazepam, 15 mg, group did not differ significantly from those receiving triazolam.</p> <p>Although not significantly different, the flurazepam, 30 mg, group had a poorer performance score and more negative mood than the other groups. Performance in this group was most improved by caffeine. In all groups, sleepiness was greatest and performance and mood (over)</p>			
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19. ABSTRACT (continued)

poorest in early morning trials and caffeine was most effective at this time.